The Effect of Particulate Air Pollution on Emergency Admissions for Myocardial Infarction: A Multicity Case-Crossover Analysis

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Ambient particulate matter (PM) air pollution has been repeatedly observed to be associated with increased risk of hospital admissions and deaths attributed to cardiovascular causes in studies conducted throughout the industrialized world (Anderson et al. 2003; Braga et al. 2001; Dockery 2001; Hock et al. 2001; Katsouyanni et al. 1996; Pope et al. 2004a; Samet et al. 2000; Zanobetti et al. 2000a).

Similar relationships have been reported in locations reflecting a wide range of PM and of gaseous pollutant concentrations (Goldberg et al. 2001; Koken et al. 2003; Linn et al. 2000; Sunyer et al. 2003; Zmirou et al. 1998). Other studies have shown that these associations are not confounded by secular time trends, seasonal patterns, influenza epidemics (Braga et al. 2000), or weather (Samet et al. 1998; Schwartz 1999, 2000). In addition, a large study of essentially every U.S. city reported that airborne particles were the only air pollutant that showed an independent effect on daily deaths, and that those gaseous air pollutants did not confound the association between PM and daily deaths (Samet et al. 2000).

Although the association of airborne particles with cardiovascular events is clear, the mechanisms behind these associations are not fully understood. To further understanding of the mechanisms behind these observations, it is important to examine associations with more specific end points that may suggest specific pathways.

Recently, attention has focused on whether particulate air pollution is a specific trigger of myocardial infarction (MI). The results of several studies of single locations assessing the effects of ambient particulate matter on the risk of MI have been disparate. We used a multicity case-crossover study to examine risk of emergency hospitalization associated with fine particulate matter (PM) with aerodynamic diameter < 10 μm (PM$_{10}$) for > 300,000 MIs during 1985–1999 among elderly residents of 21 U.S. cities. We used time-stratified controls matched on day of the week or on temperature to detect possible residual confounding by weather. Overall, we found a 0.65% [95% confidence interval (CI), 0.3–1.0%] increased risk of hospitalization for MI per 10 μg/m$^3$ increase in ambient PM$_{10}$ concentration. Matching on apparent temperature yielded a 0.64% increase in risk (95% CI, 0.1–1.2%). We found that the effect size for PM$_{10}$ doubled for subjects with a previous admission for chronic obstructive pulmonary disease or a secondary diagnosis of pneumonia, although these differences did not achieve statistical significance. There was a weaker indication of a larger effect on males but no evidence of effect modification by age or the other diagnoses. We also found that the shape of the exposure–response relationship between MI hospitalizations and PM$_{10}$ is almost linear, but with a steeper slope at levels of PM$_{10}$ < 50 μg/m$^3$. We conclude that increased concentrations of ambient PM$_{10}$ are associated with increased risk of MI among the elderly.

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admissions were traced back to 1985, ensuring at least 1 year of data before the start of the particle data.

Daily monitoring of PM10 is not done in all U.S. cities. We selected the following 21 cities with daily monitoring of PM and representing a geographic distribution across the country: Birmingham, Alabama; Boulder, Colorado; Canton, Ohio; Chicago, Illinois; Cincinnati, Ohio; Cleveland, Ohio; Colorado Springs, Colorado; Columbus, Ohio; Denver, Colorado; Detroit, Michigan; Honolulu, Hawaii; Houston, Texas; Minneapolis–St. Paul, Minnesota; Nashville, Tennessee; New Haven, Connecticut; Pittsburgh, Pennsylvania; Provo–Orem, Utah; Salt Lake City, Utah; Seattle, Washington; Steubenville, Ohio; and Youngstown, Ohio.

For most cities, the metropolitan county encompassed the city and much of its suburbs, but we used multiple counties for Minneapolis–St. Paul (Ramsey and Hennepin, MN), Birmingham (Blount, Jefferson, St. Clair, Shelby, and Walker, AL), Steubenville (Jefferson, OH, and Brooke and Hancock, WV), and Youngstown (Columbiana and Mahoning, OH).

Environmental data. We obtained PM10 data from the U.S. Environmental Protection Agency’s Aerometric Information Retrieval System (Nehls 1973). Many of the cities have more than one monitoring location, requiring a method to average over multiple locations. We computed local daily mean PM10 concentrations using an algorithm that accounts for the different monitor-specific means and variances (Zanobetti et al. 2000a). Not all cities have daily PM10 for the full range of years from 1986 to 1999; therefore, each city was analyzed for those years when daily PM10 was available.

These PM10 series had some occasional missing observations, and we replaced the missing values with the predicted values from a regression where we controlled for season and long-term trend, weather variables, and extinction coefficient, which has been shown to be a good predictor of fine particle concentrations (Ozkaynak et al. 1985). The average percentage of observations replaced was 8.4%. We obtained local meteorologic data from the U.S. Surface Airways and Airways Solar Radiation hourly data (National Environmental Satellite Data and Information Service 2003).

Analytical strategy. We investigated the association between daily PM10 concentrations and hospital admissions for MI using a case-crossover design. The case-crossover design is a variant of the case-control design to study the effects of transient exposures on acute events (Maclure 1986; Steadman 1979): AT = \(-2.653 + (0.994 \times T_d) + (0.0153 \times T_d^2)\), where \(T_d\) is air temperature and \(T_d\) is dew point temperature.

Because risk may vary nonlinearly with temperature, we used a regression spline (with 3 df) for both the same day and the previous day. PM10 was modeled linearly. To confirm the results of Braga et al. (2001), that the association was predominant with PM10 on the day of the event, we examined effects at exposure from lag day 0 to lag day 2. If we could confirm a primary association with lag day 0, we used this for the subsequent analysis described below.

As a sensitivity analysis, we tested an alternate referent selection scheme that matched on AT (rounded to the same degree Celsius) and used indicator variables to control for day of the week. Because matching on two covariates controls for interactions between the covariates, this controls for the possibility that the temperature effects vary by month. It also renders moot any question of whether the nonlinear dependence of MIs with temperature was modeled correctly. Previous day’s temperature was controlled using a cubic spline in this analysis, as well.

Case-crossover analyses lend themselves to the analysis of effect modification. Factors such as sex are controlled by matching in the design of the study, but we can still test for effect modification with interaction terms or a stratified analysis. We chose stratified analyses, because if a characteristic modifies the effect of PM10, it might also modify the effect of weather or other covariates. A stratified analysis controls for this. Specifically, we conducted stratified analyses by sex, age (< 75 vs. ≥ 75), and previous admission for chronic disease such as atrial fibrillation, COPD, CHF, and diabetes, and secondary diagnosis for pneumonia as an acute modifier.

In a second stage of the analysis, the city-specific results were combined using the multivariate meta-regression technique of Berkey et al. (1998). To be conservative, we report the results incorporating a random effect, whether or not there was a significant heterogeneity.

Finally, we assessed the shape of the dose-response relationship by fitting a piecewise linear spline, with slope changes at 20 µg/m3 and 50 µg/m3. We combined these estimates using a random effect meta-analysis as well.

Results

There were 302,453 hospital admissions for MI in the 21 cities during the study period. Table 1 shows the counts for all of the cities.
PM10, there was a 0.65% (95% CI, 0.3–1%) increase in the risk of hospitalization for MI. The average PM10 across all cities was 27 µg/m³.

We first looked at the lag structure of the association between PM10 and the risk of hospitalization for MI by simultaneously estimating the effect of PM10 from lag days 0 to 2. The combined estimates of percent change in risk (and 95% confidence interval [CI]) of emergency hospitalization for MI are shown in Figure 1 together with the estimate of lag day 0 alone. The PM10 effect is mainly associated with the change in risk on the day of hospitalization; therefore, the rest of the analysis was done for lag day 0. Figure 1 also shows the percent change of the combined estimates for PM10 at lag day 0 from the sensitivity analysis, where the control periods were chosen using the same time-stratified approach but such that exposures on the case day were compared with exposures occurring on days of the same month with the same value of AT (TEMP) as the case day.

The results shown in Figure 1 using the two different referent selection schemes are consistent and show a very similar estimated effect. Overall, we found that for each 10 µg/m³ increase in the concentration of PM10, there was a 0.65% (95% CI, 0.3–1%) increase in the risk of hospitalization for an MI among the study population. When matching by AT (TEMP) in Figure 1, we found a 0.64% (95% CI, 0.1–1.2%) increase. There was no evidence that the variation in effects size estimates by city was greater than would be expected giving their standard errors, with a chi-square value for heterogeneity of 17.8 (21 df, p = 0.6).

Figure 2 shows the results of the stratified analysis to examine effect modification by age group, sex, and previous admissions for atrial fibrillation, COPD, CHF, and diabetes and secondary diagnosis for pneumonia. We did not find a statistically significant modification of effect, but we found that acute or chronic lower respiratory disease had important effects on response to PM10. In subjects with a previous admission for COPD, we found a 1.3% change (95% CI, 0.1 to 2.8) for a 10 µg/m³ increase in PM10 in the risk of hospitalization for MI, whereas the risk was halved in subjects without a previous admission for COPD (0.6%, 95% CI, 0.3–1). In subjects with a secondary diagnosis of pneumonia, we found a 1.4% change (95% CI, 0.8 to 3.6) in the risk of hospitalization for MI, compared with a 0.6% change (95% CI, 0.3–1) in subjects without a secondary diagnosis of pneumonia. No significant heterogeneity was found when combining the stratified results.

None of the other effect modifiers we examined (age, sex, CHF, atrial fibrillation, diabetes) showed much evidence for effect modification except perhaps for sex, with a suggestive difference for males (0.9%; 95% CI, 0.2–1.6) versus females (0.5%; 95% CI, 0.05–1.97).

Finally, the shape of the exposure–response relationship between MI hospitalizations and PM10 is shown in Figure 3. The exposure response is almost linear, but with a steeper slope at levels of PM10 < 50 µg/m³.

### Discussion

We found a significant association between airborne particles and the risk of emergency MI hospitalization in a large multicity study. This association was only with PM10 on the same day, suggesting that airborne particles are acting as a trigger of an MI. We did not find evidence of effect modification by age, and weak evidence by sex, but we found a doubled risk in subjects with a secondary diagnosis of pneumonia or a previous admission for COPD, diabetes, CHF, and atrial fibrillation did not modify the risk. These results greatly expand the number of locations in which an association between PM10 and MIs has been investigated and, by using a uniform analytical strategy, provide a clearer indication of the lag between exposure and response.

The estimated effect for a 10 µg/m³ increase in PM10 on emergency MI admissions (0.65%; 95% CI, 0.3–1.0) was higher than the estimates recently published for all-cause mortality (Schwartz et al. 2003). This suggests that MI is a more specific outcome, and the lag structure found indicates a rapid pathway. In the same article (Schwartz et al. 2003), we

### Table 2. Counts of hospital admissions for MI and distribution of environmental factors.

<table>
<thead>
<tr>
<th>City</th>
<th>Years of study</th>
<th>MI events</th>
<th>Population (x 1,000)</th>
<th>AT</th>
<th>PM10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birmingham, AL</td>
<td>1988–1993</td>
<td>14,457</td>
<td>662</td>
<td>2.9</td>
<td>17.2</td>
</tr>
<tr>
<td>Boulder, CO</td>
<td>1989–1996</td>
<td>1,347</td>
<td>291</td>
<td>–4.3</td>
<td>8.0</td>
</tr>
<tr>
<td>Canton, OH</td>
<td>1989–1996</td>
<td>7,158</td>
<td>378</td>
<td>–5.1</td>
<td>8.2</td>
</tr>
<tr>
<td>Chicago, IL</td>
<td>1986–1999</td>
<td>67,974</td>
<td>5,377</td>
<td>–5.0</td>
<td>8.3</td>
</tr>
<tr>
<td>Cincinnati, OH</td>
<td>1989–1998</td>
<td>13,025</td>
<td>845</td>
<td>–3.1</td>
<td>10.9</td>
</tr>
<tr>
<td>Cleveland, OH</td>
<td>1989–1999</td>
<td>27,218</td>
<td>1,394</td>
<td>–4.2</td>
<td>9.1</td>
</tr>
<tr>
<td>Columbus, OH</td>
<td>1991–1994</td>
<td>12,451</td>
<td>1,069</td>
<td>–3.1</td>
<td>10.7</td>
</tr>
<tr>
<td>Detroit, MI</td>
<td>1986–1999</td>
<td>30,793</td>
<td>2,061</td>
<td>–4.8</td>
<td>8.3</td>
</tr>
<tr>
<td>Honolulu, HI</td>
<td>1998–1999</td>
<td>6,540</td>
<td>876</td>
<td>23.7</td>
<td>26.8</td>
</tr>
<tr>
<td>Houston, TX</td>
<td>1986–1987</td>
<td>15,085</td>
<td>3,401</td>
<td>7.8</td>
<td>23.2</td>
</tr>
<tr>
<td>Minneapolis, MN</td>
<td>1986–1989</td>
<td>14,358</td>
<td>1,627</td>
<td>–8.5</td>
<td>6.4</td>
</tr>
<tr>
<td>Nashville, TN</td>
<td>1991–1993</td>
<td>4,740</td>
<td>570</td>
<td>0.7</td>
<td>15.3</td>
</tr>
<tr>
<td>New Haven, CT</td>
<td>1988–1999</td>
<td>12,807</td>
<td>824</td>
<td>–3.6</td>
<td>8.6</td>
</tr>
<tr>
<td>Pittsburgh, PA</td>
<td>1987–1998</td>
<td>34,439</td>
<td>1,282</td>
<td>–3.6</td>
<td>9.6</td>
</tr>
<tr>
<td>Provo/Orem, UT</td>
<td>1986–1989</td>
<td>815</td>
<td>369</td>
<td>–4.1</td>
<td>7.6</td>
</tr>
<tr>
<td>Salt Lake City, UT</td>
<td>1986–1989</td>
<td>3,694</td>
<td>898</td>
<td>–4.3</td>
<td>7.6</td>
</tr>
<tr>
<td>Seattle, WA</td>
<td>1986–1997</td>
<td>12,457</td>
<td>1,737</td>
<td>1.9</td>
<td>9.2</td>
</tr>
<tr>
<td>Steubenville, OH</td>
<td>1988–1998</td>
<td>4,185</td>
<td>1,327</td>
<td>–3.6</td>
<td>9.5</td>
</tr>
<tr>
<td>Youngstown, OH</td>
<td>1989–1995</td>
<td>9,493</td>
<td>370</td>
<td>–5.2</td>
<td>7.9</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>300,167</td>
<td>25,340</td>
<td>–1.70</td>
<td>11.36</td>
</tr>
</tbody>
</table>

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also showed that the effects of PM$_{10}$ on hospital admissions for all other cardiovascular causes are not greatly different from the effects on MI admissions.

Recent studies of intermediate markers also provide support for a causal association. These include an observation of increased plasma viscosity (Peters et al. 1997) and increased plasma fibrinogen in a human exposure chamber study (Ghio et al. 2000). Results for C-reactive protein concentrations have been mixed (Brook et al. 2003; Donaldson et al. 2001; Peters et al. 2001b; Pope et al. 2004b), but PM exposure was associated with decreased plaque stability in an animal model (Zanobetti et al. 2004b), but PM$\cdot$exposure was associated with plasma viscosity (Peters et al. 1997) and these provide support for a causal association. We also did not find effect modification by sex and age, even if we found a slightly higher effect in males. The weak evidence for effect modification by age groups indicates that the adverse effect of particles is not limited to the extremely elderly population.

The indication of a somewhat higher slope at PM$_{10}$ concentrations $< 50$ µg/m$^3$ is consistent with a previous report for all-cause mortality (Schwartz 2000). Other studies have assessed exposure response for particle using nonparametric smoothing (Schwartz 1994a; Schwartz and Zanobetti 2000) or natural spline (Daniels et al. 2000) and similarly found little evidence for a threshold and more support for steeper slopes at low concentrations.

There is a substantial body of epidemiologic literature showing a clear and consistent association between concentrations of ambient PM and negative health effects (Anderson et al. 2003; Brunekreef and Holgate 2002; Dockery 2001; Katsouyanni et al. 1996; Samet et al. 2000). Less clear is the biologic mechanism by which PM could be causing this morbidity and mortality. One avenue by which investigators can offer direction is identifying which PM could be causing this morbidity and mortality. Epidemiologic research continues to narrow the focus around specific outcomes, from mortality to cause-specific mortality and from hospitalization for cardiovascular disease to MI and examination of specific modifiers.

The further epidemiologic identification of individual traits that are associated with increased risk of mortality and morbidity from increased concentrations of PM air pollution will continue to direct ongoing research into the biologic mechanism and provide critical data for risk assessment and inform policy makers.

**References**


